Chronic myeloid leukaemia

- Chronic myeloid leukaemia (CML) is a myeloproliferative stem cell disorder resulting in proliferation of all haematopoietic lineages but manifesting predominantly in the granulocytic series.
- Maturation of cells proceeds fairly normally. The disease occurs chiefly between the ages of 30 and 80 years, with a peak incidence at 55 years. It is rare, with an annual incidence in the UK of 1.8/100 000, and accounts for 20% of all leukaemias. It is found in all races.
- The defining characteristic of CML is the chromosome abnormality known as the Philadelphia (Ph) chromosome. This is a shortened chromosome 22 resulting from a reciprocal translocation of material with chromosome 9.
- The break on chromosome 22 occurs in the breakpoint cluster region (BCR). The fragment from chromosome 9 that joins the BCR carries the abl oncogene, which forms a fusion gene with the remains of the BCR. This BCR ABL fusion gene codes for a 210 kDa protein with tyrosine kinase activity, which plays a causative role in the disease as an oncogene, influencing cellular proliferation, differentiation and survival.
- In some patients in whom conventional chromosomal analysis does not detect a Ph chromosome, the BCR ABL gene product is detectable by molecular techniques.

Natural history

The disease has three phases:

- A chronic phase, in which the disease is responsive to treatment and is easily controlled, which used to last 3–5 years. With the introduction of imatinib therapy, this phase has been prolonged to longer than 8 years in many patients.
- An accelerated phase (not always seen), in which disease control becomes more difficult.
- Blast crisis, in which the disease transforms into an acute leukaemia, either myeloid (70%) or lymphoblastic (30%), which is relatively refractory to treatment. This is the cause of death in the majority of patients; therefore survival is dictated by the timing of blast crisis, which cannot be predicted. Prior to imatinib therapy, approximately 10% of patients per year would transform. In those treated with imatinib for up to 5 years, only between 0.5 and 2.5% have transformed each year

- Clinical features

Symptoms at presentation may include lethargy, weight loss, abdominal discomfort and sweating, but about 25% of patients are asymptomatic at diagnosis. Splenomegaly is present in 90%; in about 10%, the enlargement is massive, extending to over 15 cm below the costal margin. A friction rub may be heard in cases of splenic infarction. Hepatomegaly occurs in about 50%. Lymphadenopathy is unusual

Investigations FBC results are variable between patients. There is usually a normocytic, normochromic anaemia. The leucocyte count can vary from 10 to 600 × 109/L. In about one third of patients, there is a very high platelet count, sometimes as high as 2000 × 109/L. In the blood film, the full range of granulocyte precursors, from myeloblasts to mature neutrophils, is seen but the predominant cells are neutrophils and myelocytes. Myeloblasts usually constitute less than 10% of all white cells. There is often an absolute increase in eosinophils and basophils, and nucleated red cells are common. If the disease progresses through an accelerated phase, the percentage of more primitive cells increases. Blast transformation is characterised by a dramatic increase in the number of circulating blasts. In patients with thrombocytosis, very high platelet counts may persist during treatment, in both chronic and accelerated phases, but usually drop dramatically at blast transformation. Basophilia tends to increase as the disease progresses. Bone marrow should be obtained to confirm the diagnosis and phase of disease by morphology, chromosome analysis to demonstrate the presence of the Ph chromosome, and RNA analysis to demonstrate the presence of the BCR ABL gene product. Blood LDH levels are elevated and the uric acid level may be high due to increased cell breakdown.

Management

Chronic phase Imatinib, dasatinib and nilotinib specifically inhibit BCR ABL tyrosine kinase activity and reduce the uncontrolled proliferation of white cells. They are recommended as first line therapy in chronic phase CML, producing complete cytogenetic response (disappearance of the Ph chromosome) in 76% at 18 months of therapy. Patients are monitored by repeated bone marrow examination until there is a complete cytogenetic response, and then by 3 monthly real time quantitative polymerase chain reaction (PCR) for BCR ABL mRNA transcripts in blood. For those failing to respond or progress on imatinib, options include second-generation tyrosine kinase inhibitors, such as dasatinib or nilotinib, allogeneic HSCT

drugs such as hydroxycarbamide (hydroxyurea) or interferon. Hydroxycarbamide was previously used widely for initial control of disease, and is still useful in this context or in palliative situations. It does not diminish the frequency of the Ph chromosome or affect the onset of blast cell transformation. Interferon alfa was considered first line treatment before imatinib was developed. It was given alone or with the chemotherapy agent Ara C, and controlled CML chronic phase in about 70% of patients.

Accelerated phase and blast crisis

Management is more difficult. For patients presenting in accelerated phase, imatinib is indicated if the patient has not already received it. Hydroxycarbamide can be an effective single agent and low dose cytarabine can also be tried. When blast transformation occurs, the type of blast cell should be determined. Response to appropriate acute leukaemia treatment is better if disease is lymphoblastic than if it is myeloblastic. Given the very poor response in myeloblastic transformation, there is a strong case for supportive therapy only, particularly in older patients. Patients progressing to advancedphase disease on imatinib may respond to a secondgeneration tyrosine kinase inhibitor and may be considered for allogeneic HSCT.

Myelodysplastic syndrome

Myelodysplastic syndrome (MDS) consists of a group of clonal haematopoietic disorders which represent steps in the progression to the development of leukaemia. MDS presents with consequences of bone marrow failure (anaemia, recurrent infections or bleeding), usually in older people (median age at diagnosis is 69 years). The overall incidence is 4/100 000 in the population, rising to more than 30/100 000 in the overseventies. The blood film is characterised by cytopenias and abnormal looking (dysplastic) blood cells, including macrocytic red cells and hypogranular neutrophils with nuclear hyper or hyposegmentation. The bone marrow is hypercellular, with dysplastic changes in all three cell lines. Blast cells may be increased but do not reach the 20% level that indicates acute leukaemia. Chromosome analysis frequently reveals abnormalities, particularly of chromosome 5 or 7. The WHO classification of MDS.

Inevitably, MDS progresses to AML, although the time to progression varies (from months to years) with the subtype of MDS, being slowest in refractory anaemia and most rapid in refractory anaemia with excess of blasts. An international prognostic scoring system (IPSS) predicts clinical outcome based upon karyotype and cytopenias in blood, as well as percentage of bone marrow blasts. In low risk patients, median survival is 5.7 years and time for 25% of patients to develop AML is 9.4 years; equivalent figures in high risk patients are 0.4 and 0.2 years, respectively.

Management

For the vast majority of patients who are elderly, the disease is incurable, and supportive care with red cell and platelet transfusions is the mainstay of treatment. A trial of erythropoietin and granulocyte–colonystimulating factor (G–CSF) is recommended in some patients with early disease to improve haemoglobin and white cell counts. For younger patients with higher risk disease, allogeneic HSCT may afford a cure. Transplantation should be preceded by intensive chemotherapy in those with more advanced disease. More recently, the hypomethylating agent azacytidine has improved survival by a median of 9 months for high risk patients, and in the UK is recommended for those not eligible for transplantation.